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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/780,675	02/12/2001	Nicholas C. Nicolaides	01107.00098	8276

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BANNER & WITCOFF
1001 G STREET N W
SUITE 1100
WASHINGTON, DC 20001

EXAMINER	
AKHAVAN, RAMIN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/07/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action Before the Filing of an Appeal Brief	Application No.	Applicant(s)	
	09/780,675	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Ramin (Ray) Akhavan	1636	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 05/25/05 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE.

1. ☒ The reply was filed after a final rejection, but prior to filing a Notice of Appeal. To avoid abandonment of this application, applicant must timely file one of the following replies: (1) an amendment, affidavit, or other evidence, which places the application in condition for allowance; (2) a Notice of Appeal (with appeal fee) in compliance with 37 CFR 41.31; or (3) a Request for Continued Examination (RCE) in compliance with 37 CFR 1.114. The reply must be filed within one of the following time periods:
   a) ☒ The period for reply expires 6 months from the mailing date of the final rejection.
   b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection.

   Examiner Note: If box 1 is checked, check either box (a) or (b). ONLY CHECK BOX (b) WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

NOTICE OF APPEAL

2. ☐ The reply was filed after the date of filing a Notice of Appeal, but prior to the date of filing an appeal brief. The Notice of Appeal was filed on _____. A brief in compliance with 37 CFR 41.37 must be filed within two months of the date of filing the Notice of Appeal (37 CFR 41.37(a)), or any extension thereof (37 CFR 41.37(e)), to avoid dismissal of the appeal. Since a Notice of Appeal has been filed, any reply must be filed within the time period set forth in 37 CFR 41.37(a).

AMENDMENTS

3. ☐ The proposed amendment(s) filed after a final rejection, but prior to the date of filing a brief, will not be entered because
   (a) ☐ They raise new issues that would require further consideration and/or search (see NOTE below);
   (b) ☐ They raise the issue of new matter (see NOTE below);
   (c) ☐ They are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
   (d) ☐ They present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____. (See 37 CFR 1.116 and 41.33(a)).
4. ☐ The amendments are not in compliance with 37 CFR 1.121. See attached Notice of Non-Compliant Amendment (PTOL-324).
5. ☐ Applicant's reply has overcome the following rejection(s): _____.
6. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
7. ☐ For purposes of appeal, the proposed amendment(s): a) ☐ will not be entered, or b) ☐ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.
   The status of the claim(s) is (or will be) as follows:
   Claim(s) allowed: _____.
   Claim(s) objected to: _____.
   Claim(s) rejected: _____.
   Claim(s) withdrawn from consideration: _____.

AFFIDAVIT OR OTHER EVIDENCE

8. ☐ The affidavit or other evidence filed after a final action, but before or on the date of filing a Notice of Appeal will not be entered because applicant failed to provide a showing of good and sufficient reasons why the affidavit or other evidence is necessary and was not earlier presented. See 37 CFR 1.116(e).
9. ☐ The affidavit or other evidence filed after the date of filing a Notice of Appeal, but prior to the date of filing a brief, will not be entered because the affidavit or other evidence failed to overcome all rejections under appeal and/or appellant fails to provide a showing a good and sufficient reasons why it is necessary and was not earlier presented. See 37 CFR 41.33(d)(1).
10. ☐ The affidavit or other evidence is entered. An explanation of the status of the claims after entry is below or attached.

REQUEST FOR RECONSIDERATION/OTHER

11. ☒ The request for reconsideration has been considered but does NOT place the application in condition for allowance because: See continuation sheet.
12. ☐ Note the attached Information Disclosure Statement(s). (PTO/SB/08 or PTO-1449) Paper No(s). _____
13. ☐ Other: _____.

5.00

CONTINUATION SHEET (PTOL-303 Form):

Applicant's request for reconsideration has been fully considered but is not deemed persuasive. Applicant asserts that the specification provides ample written description for the genera of any truncated PMS2, any PMSR and any PMS2L mismatch repair proteins (MMR), where said proteins represent a critical structural element, whereby expression of said proteins in bacterium must correlate to a dominant negative effect resulting in hypermutability. More particularly, Applicant asserts: (1) the specification provides four species of MMR proteins (Remarks, p. 3, third full paragraph) in three strains of bacteria; (2) members of the recited MMR protein families share a common structural feature – homology to the 134 N-terminal amino acids of PMS2 protein (Remarks, p. 4, ¶ 1); and (3) the cited art provide no reason to doubt that substitution of any species of truncated PMS2, any PMSR or any PMS2L protein would function as dominant negative mismatch repair in any bacterium (Remarks, p. 6, last ¶, bridging to p. 7). Each of Applicant's arguments is discussed in turn.

The specification does not provide sufficient description for a representative number of embodiments of MMR proteins. Applicant asserts that four embodiments of MMR proteins (hPMS2-134, *A. Thaliana* PMS2-134, PMSR2 and PMSR3) are demonstrated to cause hypermutability in three strains of bacteria (BL21, DH5α and DH10B). First, the three strains of bacteria are all strains representing a single species of bacterium (i.e., gram negative, *E. coli*). Regarding, PMS2-134 truncations from any source (e.g., human, plant, etc.), there is no support in the specification or in the prior art that said truncations will confer hypermutability in all species of bacterium (e.g., gram positive). For example, to date, there is no structure-function relationship that has been identified in gram-positive bacteria for MutL (i.e., PMS2) homologues.

If said relationship is unknown for PMS2 homologues in gram-positive bacteria, it logically follows that results obtained for PMS2-134 are not necessarily extendable to all species of bacteria (e.g., expression of PMS2-134 in gram-positive). In addition, it should be noted that the broadest claims are directed to *any* truncation of PMS2. In other words, the broadest claims are not limited to PMS2-134, but to any truncated form of any PMS2, thus further expanding the number of potential species encompassed in the genus of PMS2 truncated proteins from any source. There is no support in the specification or in the relevant art for *any* truncated PMS2 (e.g., clarification of truncation mutations wherein said dominant negative truncated PMS2 protein, when expressed, confers hypermutability). In sum, while the MMR system proteins have been extensively studied in gram-negative bacteria, such as *E. coli*, comparatively little is known about the role of such proteins in gram-positive bacteria.

Regarding any PMSR or any PMS2L protein, the specification is equally lacking in providing a sufficient description of a representative number of genes encoding said proteins that when expressed in any bacteria will confer hypermutability. Applicant asserts that the structural feature that confers hypermutability (e.g., when dominant negative MMR proteins are expressed) is homology to the 134 N-terminal amino acids of the PMS2 protein. (e.g., Remarks, p. 4, ¶ 1, bottom). It is respectfully pointed out that merely identifying a gene with structural similarity does not automatically correlate to functionality, as is apparently being implied. On a first order, structural similarity may suggest a functional role in an MMR system. (e.g., Kondo et al. J. Biochem. 1999; 125:818-25; p. 819, col. 1). However, it is wholly separate proposition to assert that any PMS2L or PMSR gene, which may be from any source and expressed in any bacteria, will confer hypermutability.

As is evidenced in the relevant art, there is a significant level of unpredictability regarding structure to function correlation (i.e., genes encoding proteins imparting hypermutability when expressed in bacteria). For example, even when limited to a single source (i.e., human) of MMR genes, the total number of PMS2L genes is unclear, *as are the functions of their protein products*." (Id. at p. 822, col. 2; emphasis added). The instant specification merely points out that PMS2L genes are homologous to PMS2 gene and nothing more. (p. 18, ll. 8-16). Regarding PMSR, a single gene (i.e., human PMSR3) is expressed in *E. coli* cells. As stated above, mere homology does not equate to functionality. In sum, the specification does not sufficiently describe species within the genera of PMS2 truncations, PMSR or PMS2L genes encoding a dominant negative mismatch repair protein that confers hypermutability in any bacteria when expressed therein.

Applicant's next argument is predicated on the assumption that mere homology is predictive of function regarding any PMS2 truncation, any PMSR gene and any PMS2L gene. As stated above and as is evidenced by knowledge in the art, mere homology does not fill in the gap with respect to the lack of information in the instant disclosure and in the art. With respect to PMS2 truncations, only the total number of amino acids encoding a particular PMS2 gene (e.g., truncation variants) limits the genus of MMR proteins. Only a single truncation variant is disclosed (i.e., PMS2-134). The knowledge in the art appears to be limited to the same variant. Therefore, one cannot readily envisage additional PMS2 truncations, whereby expression of the same induces hypermutability in any species of bacteria.

Applicant's final assertion is that the cited art does not undercut the proposition that any PMS2 truncation, any PMSR or any PMS2L protein when expressed in any bacteria will induce

hypermutability. With respect to the Prudhomme reference, Applicant asserts that the proteins disclosed are not analogous to the truncated PMS2 protein. This may be true. However, the claims are not merely limited to PMS2 truncations (i.e., PMSR and PMS2L). The PMSR and PMS2L are *full-length* homologues to the N-terminal portion of PMS2, which is itself a MutL homologue. Prudhomme teaches that expression of *Streptococcus pneumoniae hex*B – a *full-length* homologue to MutL – does not induce hypermutability. It follows, there is unpredictability regarding hypermutability, whereby expressing MMR proteins that share homology to PMS2 comprises a genus of critical structures linked to the prescribed functionality of inducing hypermutability. The lack of interchangeability between structures is further exacerbated by the fact that there appears to be a differential with respect to structure/function correlation depending on the bacterial cell wherein expression occurs (e.g., gram-positive versus gram-negative bacterium). Therefore, one of skill would not necessarily expect any PMS2L from any organism when expressed in any bacteria to also function as a dominant negative mismatch repair protein.

With respect to the Kondo reference, Applicants assert that the reference teaches that PMS2Ls are homologous in structure to human and *A. thaliana*. Applicant asserts that, "Kondo further provides that the [any] PMS2L proteins are functionally similar to PMS2-134 because they do not bind MLH1. Thus, Kondo's teachings weigh in favor of applicants' assertion that PMS2L proteins exert a dominant negative effect on MMR in bacteria." (Remarks, p. 6, middle ¶). Applicant appears to be suggesting that it would have been obvious to one of skill that PMS2L expression would induce a mutator phenotype, similar to PMS2-134. However, as stated above, mere homology does not necessarily correlate to functionality.

For example, MMR proteins may not function similarly in repair of mismatched DNA (e.g., strand discrimination in eukaryotes not utilizing DNA methylation versus prokaryotes). In any event, given that the genus of PMS2L genes is vast and given that the claims are not delimited to any degree with respect to percent identity to any PMS2 gene, one of skill cannot envisage a sufficient number of embodiments for the genus of PMS2L proteins that must correlate to a mutator phenotype in any bacteria. As Kondo states:

> "Since PMS2Ls carry a highly conserved amino-terminal domain, they *may* also be involved in the downstream pathway of the human MMR system or they *may have completely different role(s) in the cell.* If the former *possibility* is true, the abnormal expression of some PMS2Ls *may give rise to defects in the MMR pathway* [hypermutability]." (p. 824, col. 2, last ¶; emphasis added)

In view of what is stated above and the foregoing passage, one of skill cannot deem the instant specification to provide a representative number of species encompassed by the genus of PMS2L genes.

With respect to Nicolaides, Applicant similarly asserts that PMSR genes are related to PMS2 genes, thereby should be expected to function as dominant negative mutator phenotype proteins. The same analysis provided above is equally applicable here. Mere homology is not necessarily predictive of functionality in any species or genus of bacterium. For example, a single amino acid residue change may induce an altogether distinct secondary or tertiary protein structure, thereby conferring a different functionality. In sum, the instant disclosure does not provide a representative number of embodiments with respect to the genera of genes encoding PMS2 truncations, the PMS2-134 truncations expressed in any bacteria, the PMSR and the PMS2L proteins, so as to indicate to one of skill that Applicants were in possession of the claimed genera.

Further, it is noted that Applicant requests that the provisional double patenting rejection be held in abeyance. As the outstanding rejections are maintained, the provisional double patenting rejection is not the only remaining issue, thus is not held in abeyance.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ray Akhavan whose telephone number is 571-272-0766. The examiner can normally be reached between 8:30-5:00, Monday-Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, PhD, can be reached on 571-272-0781. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Respectfully submitted,

Ray Akhavan/AU 1636

DAVID GUZO
PRIMARY EXAMINER